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Fragile X Mutation and FG Syndrome-Like Phenotype

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We present data on 4 mentally retarded brothers, 2 of whom were dizygotic twins with congenital hypotonia, constipation, head size disproportionately large for length or height, and a combination of minor anomalies suggestive of FG syndrome. These brothers have a mentally retarded full sister with similar minor anomalies and an older half-brother with the Martin-Bell syndrome. The mother is mentally retarded; 4 of 7 individuals are positive for fragile X, but all have a CGG expansion ranging from 0.2–2 to 4 kb. Although the phenotype is not completely typical of the FG syndrome and the coincidence of the FMR1 mutation and segregation of the MCA/MR phenotype are highly unlikely, the FMR1 mutation may affect morphogenesis more extensively and differently than the Martin-Bell syndrome does to effect an FG syndromelike phenotype in certain families. This phenotype does not appear to be a contiguous gene syndrome, but an effect of the FMR1 mutation on an adjacent gene must be considered.

KEY WORDS: fragile X, FG syndrome, X-linked mental retardation, hypotonia, macrocephaly

INTRODUCTION

The X-linked recessive FG syndrome was first described by Opitz and Kaveggia [1974] and named with the initials of the index cases. Opitz and Kaveggia reported on 5 mentally retarded males, 3 brothers and 2 first cousins, with congenital hypotonia, relative macrocephaly, distinctive face, imperforate anus, and behavior disturbances. Additional familial observations were published [Keller et al., 1976; Riccardi et al., 1977], which reported many additional manifestations and extended the FG phenotype; therefore, delineating the cardinal manifestations of this MCA/MR syndrome more accurately became necessary, as was done by Opitz et al. [1982, 1988] and Thompson and Baraitser [1987]. The association of fragile X (fra(X)) syndrome and an FG-like phenotype was reported in 6 of 10 carriers or affected members of a fra(X) family presenting with a variable combination of FG traits, such as epilepsy and mental retardation [Loesch et al., 1992]; more recently, imperforate anus was observed in an atypical fra(X) phenotype due to an FMR1 deletion [Quan et al., 1995].

MATERIALS AND METHODS

Clinical data were collected in Picardie and in the Centre de Génétique Clinique of the University of Amiens (C.P.). Fra(X) screening studies were performed by analyzing at least 100 metaphases of M199 cultures and confirming the presence of a fragile X chromosome with G and R banding in the Center for Human Genetics (J.P.F.) at the University of Leuven (values below 2% are considered nondiagnostic in this laboratory).

DNA was extracted from peripheral blood lymphocytes with standard techniques. Southern blotting was performed after double ECORI EagI digestion and by using Stb 12.3 as a probe [Rousseau et al., 1994]. Expansion of the CGG repeats was expressed as deltas (Δ) to indicate the increase in repeat size as compared with a sample of pooled normal controls. Expansion of the fra(X) E repeat was not studied.

RESULTS

II-4 and II-5

Twin brothers were referred at 6 years of age because of mental retardation and minor anomalies. They were born to nonconsanguineous parents at 37 weeks of gestation after a normal twin pregnancy. Delivery was normal. Birth weights were 3,180 and 2,750 g (50th and 25th centile), lengths were 48 and 45 cm (<10th centile), and occipito-frontal circumferences (OFCs) were 35 and 34 cm (75th and 50th centile). Both boys were severely hypotonic from birth, and seizures had started in early infancy. At 6 years old, the boys were severely retarded and nonambulatory. They presented with epilepsy, short attention span, and few purposeful movements. They required assistance in eating and dressing. They could smile and have eye contact, but vision was poor, with nystagmus and strabismus. Fundi were normal. Electroencephalography was abnormal, with diffuse sharp waves and episodes of spikes and waves.

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Speech development was absent but hearing was normal. Auditory brainstem responses, sensory and motor evoked potentials, and nerve conduction velocity were normal. Results of routine biochemical screening including amino acids, organic acids, and very long chain fatty acids (VLCFA) were normal. Chromosomes (peripheral blood lymphocytes) were normal (46,XY). Computed tomography (CT) of the brain showed slightly enlarged ventricles and moderate cerebral atrophy. The facial appearances suggested FG syndrome: high and broad forehead, prominent occiput, temporal balding with high frontal hairline, apparently low-set posteriorly angulated ears, down-slanting palpebral fissures, depressed nasal bridge, short nose with anteverted nares, thick philtrum and upper lip, diastema between central upper incisors, high arched palate, and everted lower lip (Fig. 1). Testes were 15 × 5 mm in II-4 and 10 × 5 mm in II-5 (normal for age: 15 × 10 mm, i.e., ≤1 ml ± 0.4 SD). The boys had a mixed hyperactive, friendly and aggressive behavior, and IQ was below 40 in both. Other anomalies were severe constipation, sacral dimple, right club foot, and a +1.5 SD macrocephaly in early infancy in II-4 and hypoplastic thumbnails in II-5, which was also present in the father.

II-6

A younger brother was born at 40 weeks by forceps extraction after a normal pregnancy. Birth weight was 4,060 g, length was 51 cm, and OFC was 38 cm (>97th centile). The neonatal period was complicated by respiratory distress. In the first months of life, the same striking phenotype became evident: frontal bossing, thin and sparse hair, cowlick, apparently low-set and abnormally modeled pinnae, hypertelorism, strabismus, distinctive face with drooping and open mouth, thick philtrum, and diastema of the upper incisors. He had bulging eyes, with bluish sclerae and large corneae (Fig. 2), a cavernous hemangioma of the lower lip, hand anomalies including a bilateral postaxial polydactyly type B with pedunculated postminimi, a sacral dimple, 15-×-10-mm testis, and hypoplastic thumbnails, which the father also had. The examinations performed on the twins were performed on the younger brother, with normal results. CT of the brain showed moderate cortical atrophy. At 2 years of age, psychomotor development was severely retarded with hypotonia, clonic seizures, IQ below 50, and constipation. Macrocephaly (+3 SD) was still evident. The boy had adequate head control and was able to crawl and roll over, but he could not sit without support or walk independently. Visual and social contacts were poor. In addition, he had rumination and motor stereotypies.

II-7

The youngest brother II-7 (Fig. 3) was born at 39 weeks after a normal pregnancy. There was relative macrocephaly (birth weight = 3,900 g, length = 50 cm, OFC = 36 cm). At 1 year of age, he closely resembled his brothers, with postnatally decreasing macrocephaly

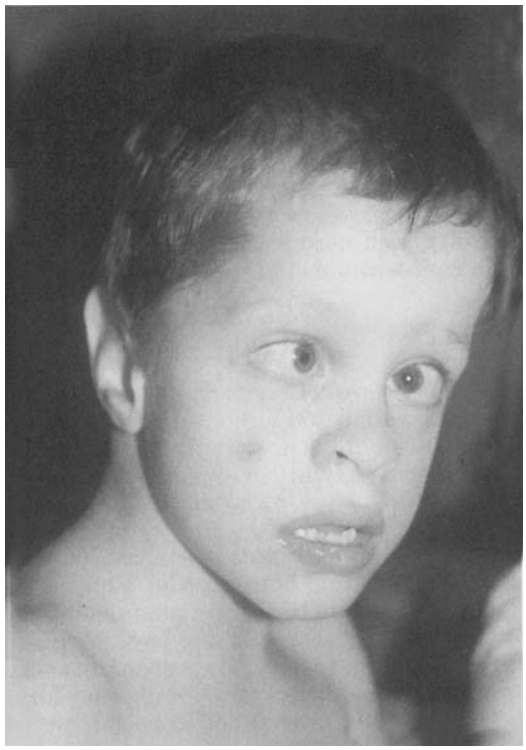

Fig. 1. Patient 2 (II-5): frontal bossing, strabismus, short broad nose and anteverted nares, open mouth with thick philtrum, prominent upper lip, anterior crowding of the teeth, and everted lower lip.

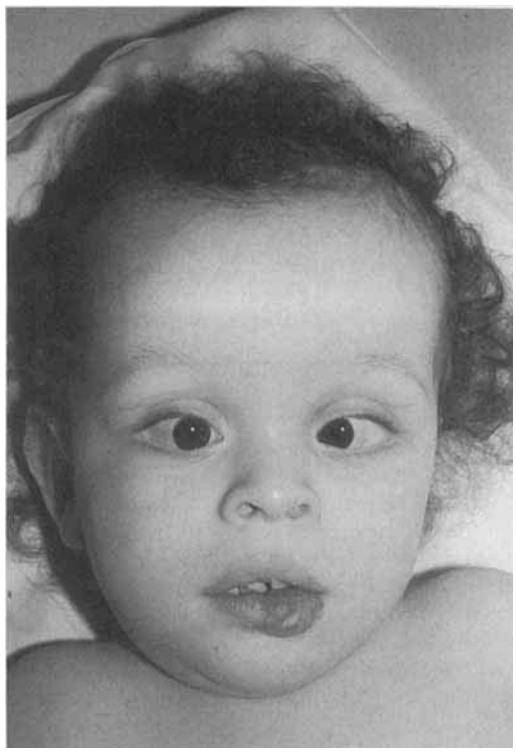

Fig. 2. Patient 3 (II-6): macrocephaly (+3 SD), wide forehead, high anterior hairline, temporal balding, hypertelorism, strabismus, large corneae, blue sclerae, broad nose with depressed nasal bridge, thick philtrum, diastasis between central incisors, arched palate, and cavernous hemangioma of the lower lip.

(+0.9 SD), temporal balding, cowlick, apparently low-set posteriorly angulated ears with poorly modeled helices (Fig. 4), bulging forehead and eyes, blue sclerae, short nose with depressed nasal bridge, prominent upper lip, facial hypotonia with open mouth, small chin, and 11-×-8-mm testis. The boy had a sacral dimple and his thumbnails were hypoplastic. He had no head control and was extremely hypotonic with constipation and poor suck and feeding (IQ was not evaluated). He was able to fix on, but did not reach for objects, and he could not sit unaided. He often had short episodes of blinking and leg jerking that alternated with brief staring spells that resembled seizures. Electroencephalography was abnormal, with excess delta and theta slow wave activity and episodes of spikes and waves that were more predominant in the left hemisphere. Unlike his older brothers, his behavior was unremarkable.

Patient II-3

The only sister of these 4 brothers was admitted twice to the Paediatric Hospital for an allergic reaction and then for suspicion of child abuse. Psychomotor development was moderately retarded from psychosocial deprivation. She was hypotonic in the first month of life, could sit without support at 9 months, took her first steps at the age of 15 months, and walked at 17 months. At school, major learning problems were evident. Clinical examination showed frontal bossing, downward slanted palpebral fissures, blue sclerae, depressed nasal bridge and high arched palate, and pectus excavatum, as seen in her brothers.

Family Data (Fig. 3)

The father (I-4) had mild mental retardation but no minor anomalies except for the hypoplastic thumbnails that were also present in his sons II-5, II-6, and II-7. The mother was phenotypically normal but mentally retarded and had emotional problems. She gave birth to two older sons (II-1 and II-2) from 2 other fathers: II-2 was normal and II-1 at 12 years was mentally retarded. His phenotype, which was different from that seen in his 4 half-brothers (II-4, II-5, II-6, II-7) and his half-sister (II-3), was very suggestive of the diagnosis of fra(X) syndrome, with his narrow face, large ears, prominent forehead, prognathism, pectus excavatum, macroorchidism (30 × 15 mm), and an IQ of 50. Fra(X) examination was performed in the mother (I-3) and her 7 children. The results of cytogenetic data and molecular findings are given in Fig. 2. The fragile X study was positive in the mother (I-3), her mentally retarded son (II-1) and daughter (II-3) and in her 4 sons (II-4, II-5, II6, II-7) with FG syndromelike phenotype. II-1 was a mosaïc male with a premutation (Δ: 0.2 kb) and a 2-kb smear methylated full mutation. Because of serious behavior problems, no biological sample was available on the father (I-4). II-6 was negative at the cytogenetic fra(X) screening, as are 2–3% of fully mutated males tested in the laboratory.

DISCUSSION

The 4 affected brothers of this fra(X) family displayed in the first year of life at least 11 clinical symptoms compatible with the diagnosis of FG syndrome: family data consistent with X-linked inheritance, distinct facial anomalies, relative macrocephaly, high frontal hairline and broad forehead, congenital hypotonia and strabismus, joint laxity, feeding problems and constipation, and severe developmental delay with seizures and hyperactive behavior. However, in typical FG syndrome, congenital hypotonia is severe and often responsible for poor suck, feeding difficulties, and respiratory complications [Thompson et al., 1985] and can lead to joint contractures. CT scan of the brain may show mild cortical atrophy, severe postnatal microcephaly or partial agenesis of the corpus callosum [Lacassie et al., 1986: Thompson et al. 1986: Proud et al., 1982: Kato et al., 1994]. In some families, one or more affected males lacked either mental retarda-

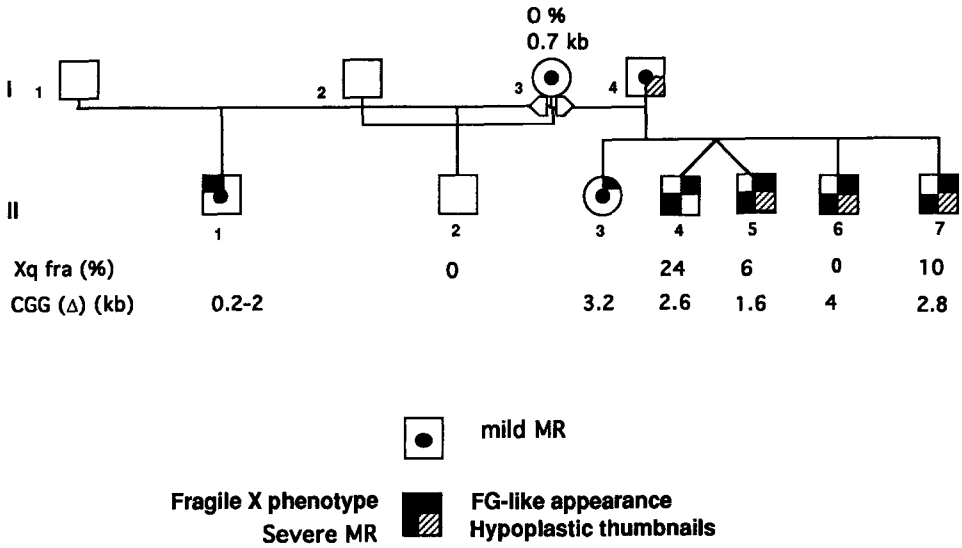

Fig. 3. Pedigree of the family.

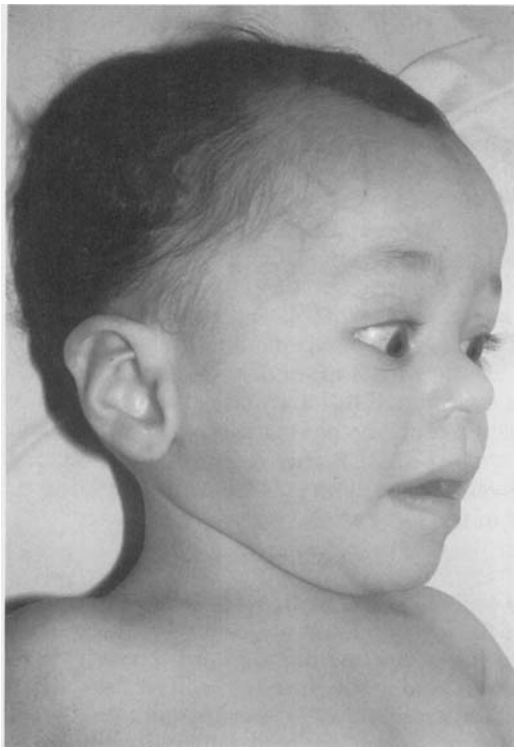

Fig. 4. Patient 4 (II-7): cowlick, bulging eyes with blue sclerae and down-slanting palpebral fissures, posteriorly rotated ears and prominent antihelices, short and saddled nose, prominent philtrum and upper lip, arched palate, and open-mouthed expression.

tion [Opitz et al., 1988: Sarda et al., 1989], hypotonia [Kato et al., 1994], or gastrointestinal manifestations [Thompson and Baraltser, 1987; Opitz et al., 1988], which creates a diagnostic problem especially in sporadic cases. Moreover, minor and nonspecific abnormalities have been observed in limbs, skeleton, skin cardio-vascular system, kidneys and gastro-intestinal tract, which contribute to the very broad phenotype of the FG condition, as does the variability of the clinical expression between families [Thompson et al., 1989].

In Fragile X syndrome, 15 to 20 % of effected males display a severe mental retardation in early childhood associated with hypotonia, constipation, seizures or minor limb malformations [Hagerman et al., 1983] overlapping with other XLMR syndromes. More recently two associations of FG-like symptoms were reported. In a family, prominent forehead, high hairline with frontal upsweep (cowlick), flared nostrils, cleft lip and/or palate, thick lips, micrognathia, abnormal fingers and toes, hypotonia, joint contractures and epilepsy were observed in 6 of the 10 carriers or affected patients with 0 to 39 % fragile X and Pst fragment sizes ranging from 1 to 3.2 kb and minor limb anomalies were found in an unaffected male relative [Loesch et al., 1992]. In the second observation, an imperforate anus was diagnosed shortly after birth in an atypical Prader-Willi like phenotype due to a >9 Mb deletion of FMR1 and of the flanking DNA, which could suggest that deleted genes proximal to the FMR1 locus could be responsible for this unusual fragile X phenotype [Quan et al., 1995].

The findings in the affected sibs of the present fragile X family illustrate the difficulties of nosological classification on a clinical basis only. Indeed, a paternally inherited autosomal dominant disorder with decreased penetrance cosegregating with FRAXA (CGG) repeat expansion cannot be completely ruled out. As suggested by the observation of Loesch and Quan, there is nevertheless a strong possibility that the symptoms are either related to an atypical expression of the FG syndrome due to the simultaneous expression of the fragile X condition present in the family, or more likely due to a rare form of pleiotropy of this FMR1 mutation. Whatever the answer, this problem will be solved only by future analysis of segregation or the isolation of a candidate gene for FG syndrome.

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